**Useful IRB Protocol and Template Language that is consistent with CAHBIR SOPs**

**General Risks of MRI:**

Protocol Template language:

There are no known health risks associated with the magnetic field produced by this 3.0T scanner in healthy adults. The FDA has indicated that they consider MR imaging on machines up to 4.0T to pose no risk (https://www.fda.gov/medical-devices/cdrh-research-programs/magnetic-resonance-imaging-mri-safety-and-effectiveness). Sammet (2016) provides discussion of MRI safety issues, each of which can be avoided with proper management. These include:1) attractive forces and torque caused by the magnet, 2) thermal effects caused by the radiofrequency fields, 3) peripheral nerve stimulation due to switching gradients, 4) hearing damage caused by the acoustic noise of the gradient system, 5) questions of risk for a fetus, 6) claustrophobia and other discomforts. These are briefly detailed below.

*Attractive Forces*: Ferrous material can be pulled toward the magnet, causing injury to a subject. These forces can cause metallic implants to be attracted to the magnet. The magnet can erase credit cards and other types of swipe cards.

*Thermal Effects*: The radiofrequency field can cause heating of ferrous material that are in the field, this is a concern for metal implants, and tattoos on the skin that specifically contain metal (iron).

*Peripheral Nerve Stimulation (PNS)*: Although none of the planned scans involve parameters that should cause any peripheral nerve stimulation (tingling sensation caused by stimulation of a sensory nerve or motor twitch caused by stimulation of a motor nerve), it is hypothetically possible for this to occur in a scan in which magnetic gradients are being rapidly switched because the gradient cause a neuron near the surface of the skin or muscle to “fire”. While the gradient performance of the magnet is not expected to produce PNS within the operational limits defined by Siemens, they remain a possibility for a small minority of sequences. Note that PNS is not considered an adverse event because when it occurs, it is an issue only of patient comfort rather than a safety concern.

*Hearing damage*: The gradient system noise often reaches 100dB. Sustained exposure to this volume of noise without noise reduction devices can cause hearing damage.

*Claustrophobia, and Additional Discomforts:* Some participants experience anxiety due to the enclosed nature of the space in the scanner and head coil. Some potential minor discomforts associated with the procedures include back discomfort from lying in one position.

Individuals must complete an MRI screening form, which includes private health information. They may have some psychological discomfort disclosing this information. There would be a confidentiality risk if such information were not treated in a protected confidential manner. During the course of scanning an incidental finding could be detected. Individuals might experience stress or anxiety if such an incidental finding is reported to them.

* **Existing Condition/Disorder**

Although 3.0 T MRI is safe for healthy individuals several existing conditions, or situations can increase risk, or can increase the risk of discomfort. Persons at primary risk from exposure to the magnet include persons with metal surgical implants, and anyone with implanted electric/magnetic devices (e.g. a pacemaker, aneurism clips, IUDs). Additional risks include individuals with any other pieces of metal (filings, shavings, jewelry that cannot be removed) from their body. Note: metal in bone (such as pins) provide minimal risk if outside of the magnet bore, but are excluded from this protocol unless the material is known to be nonferrous (e.g. titanium) or considered safe by the *Reference Manual for Magnetic Resonance Safety. Implants and Devices*, 2020 Edition. Metal in fillings are permissible, but individuals with braces and metal retainers are excluded from this protocol. Individuals with metal in their eye would be placed at risk for eye damage if exposed to the magnet, and individuals with iron or lead based tattoos are at risk for the tattoo area to heat up during the scanning process. Claustrophobia and chronic (or recent acute) back pain can be an additional risk factor for discomfort given the need to lie still within an enclosed space during the scan.

* + - **Minimizing Risks**

*Exclusion of individuals with contra-indications for scanning*: Individuals at primary risk for the exposure to high magnetic fields due to the presence of potentially dangerous ferrous materials in the body are excluded. This eliminates the risk of attractive forces or thermal heating. Participants are told of these exclusions during recruitment and must complete a comprehensive screen of any potential metal on their body. This screening form is reviewed by a member of the team with level 2 training, and it is confirmed by the scanner operator before the participant is allowed in the scanner room. For participants who possess orthopedic screws or pins that are firmly in bone, participants can only be scanned if the type of screw or pin is considered safe according to the *Reference Manual for Magnetic Resonance Safety. Implants and Devices, 2020 Edition* Participants are withdrawn from the study if it is determined there is any contra-indication for scanning.

*Avoidance of other risks from the high magnetic field*: The MRI suite is coded in terms of zones. The entire scanner suite has controlled access, and only individuals with appropriate training (see staff training) are allowed to permit people into the scanner control room or MRI and only after they have been screened. Subjects are reminded to remove any jewelry before entering the scanner room and are screened with a handheld metal detector before entering the scanner room. Subjects are given a box/locker to place their wallet, keys and other personal belongings before entering the scanner room. All study personnel have undergone safety training and must adhere to safety rules to limit potential risks in the scanner suite.

*Avoidance of claustrophobia*: Participants are excluded if they report a history of claustrophobia, and they are warned in advance that the space is cramped and that they will have a head coil placed around their head. A picture of a person in a head coil will be present on the webpage listing the exclusions for the study. If an individual does become claustrophobic during the scan, they can inform the study staff and discontinue the study at any time.

*Avoidance of physical discomfort from lying in the scanner*: Individuals with a history of chronic or recent acute back pain are excluded from the study. Subjects are warned that they will need to lie on their back in a still position for up to 90 minutes. Pillows and cushions are used to keep the subject comfortable and the scan operator always checks that the person is comfortable before closing the scan room door. If the subject does need to move during the scan, they can be repositioned as long as it is done between scans.

*Avoidance of discomfort from volume* of the scanner: Subjects are given earplugs and noise reducing headphones to limit the volume of the scanner.

*Avoidance of psychological discomfort related to exposure of private health information:* The screening form is reviewed in a quiet room within the CAHBIR to avoid any violations of confidentiality and minimize subject psychological discomfort. The information is then placed in a locked cabinet that is only accessible to study staff.

ICD template language:

Exclusion criteria “MRI scanners of the type used in this study have never been shown to have any adverse health effects for healthy persons. However, because of the strong magnetic field inside the scanner, you cannot participate if you have any metal devices or metal fragments in your body such as bullets or shrapnel. Persons who have life-support devices made of metal (e.g. pacemakers and aneurysm clips), metal prosthetic devices (such as “fake” legs that cannot be easily removed) or other metallic implants (e.g. cochlear implants, IUDs) cannot be included in this study. Individuals who have had eye injuries involving metal fragments and individuals who have welded metal without eye protection must also be excluded because they may have metal specks embedded in their eyes. If you have metal pins or screws in bones in your arm, hands, hip, leg or foot, or back you may be able to participate, but you need to tell this to the researchers, as they will need details. The researchers will need to verify whether or not you can participate depending upon the nature of the pins or screws. If the safety of the pin or screw cannot be determined, you will be excluded from the study. Individuals with metal-based tattoos are also excluded.

Under who may take part in the study, the following may be included.

In addition, those with a current pregnancy, or any of the following contra-indications for MRI should **not** participate:

* Ferrous (iron) material implanted in or on the body, including flakes or filings, surgical clips, bullets, or electrical devices such as a pacemaker, or nonremovable ferrous jewelry (fillings in teeth and permanent retainers are permitted)
* Fillings and permanent retainers do not provide a safety risk and are not general exclusions. However, upper retainers may interfere with image quality and therefore are an exclusion
* Individuals with surgical pins or plates above the neck are excluded. Surgical pins or plates below the neck are exclusions, except when the material is fixed to bone, and considered acceptable. Almost all recent orthopedic implants are made of materials that are not ferromagnetic and therefore are safe for scanning, and even though some screws are still made of ferromagnetic materials these are firmly screwed into bone. In cases where the material is unknown or deemed unsafe for scanning, the participant will be excluded*.*
* History of eye injury involving metallic materials, shavings in eyes, or welding without a face mask
* Lead/iron tattoos on the neck or face.
* Claustrophobia (history of significant anxiety in closed places)
* Back problem that would prevent you from laying still comfortably for up to 90 minutes
* History of head trauma or neurosurgery. Current or past neurological disorder (other than headaches or peripheral nerve disease)

And under risks in the ICD

MRI Risks: There are no known health risks associated with the magnetic field produced by the scanner in healthy adults. Exposure to high magnetic fields is associated with primary or secondary risks in certain patient populations (e.g., patients with pacemakers), therefor such patients are excluded. Subjects with aneurysm clips, neural stimulators, possible metal fragments in the eyes, cochlear implants, artificial cardiac valves, iron based facial tattoos, and body piercings that are not removable are also excluded from participation. The only other risks associated with scanning are claustrophobia while in the magnet, physical discomfort from lying still in the magnet, and the loud sound of the magnet. Screening interviews and the MRI screening questionnaire are used to rule out the presence of any medical or neurological problems that would cause a risk in the magnet.

**MRI Pregnancy Risk**:

Women who are known to be pregnant are not scanned for research purposes at CAHBIR.

Studies may choose to have all women of childbearing potential completed a urine pregnancy test, or may allow them the option to sign a pregnancy waiver if they are not being tested. Template language appears below, and a template for inclusion with a consent document is available on the CAHBIR website.

Template Protocol language pregnancy regarding risk.

*Effect on an unborn child*: At present there is no evidence that exposure to an MRI places an unborn fetus at any risk. However, to avoid concerns about such a risk, females are excluded from participating if they are currently pregnant. Furthermore, women are given the opportunity to take a urine pregnancy test prior to scanning, and the scan will be cancelled if they test positive. This test is conducted in a private bathroom that is part of the CAHBIR suite to maintain privacy, and the results of the test are discussed in a private room. Because many female subjects know that they are not pregnant (and may not be of childbearing potential), female subjects can opt to sign a document indicating that they understand the risks and have waived having a pregnancy test. A positive urine pregnancy test might cause the subject psychological discomfort if the pregnancy is unwanted. However, that distress would almost surely occur on its own, as they would eventually find out that they were pregnant, and indeed, finding out sooner than later is typically advantageous in such cases.

Pregnancy Testing Waiver Template should be included with consent documentation if allowing a waiver, and is available on the CAHBIR website.

**Incidental Findings**

Incidental findings can arise in research studies. CAHBIR has attempted to balance the ethical need to evaluate potential incidental findings and inform participants of findings that warrant clinical attention, with the cost and time demands of performing a neuroradiologist evaluation of scans. CAHBIR’s default approach is to have the staff MRI Technologist review anatomical scans for evidence of incidental findings, and if one is observed to have the de-identified data transmitted to University Radiology Group (URG) for evaluation by a neuroradiologist. Please note URG is not a research collaborator on individual studies, but rather is contracted with the University to provide a service for all studies conducted at CAHBIR.

In such cases CAHBIR assumes the cost of the read.

Two deviations from the default are allowed.

1. In studies of populations with an elevated risk of incidental findings, the IRB may require that scans from every subject are evaluated by a neuroradiologist for incidental findings. In such cases, an extra $50 will be added per scan to provide the read if using the URG service.
2. A study may assume responsibility for evaluation of incidental findings. In such cases, researchers can expect that the IRB will require them to have a member of the study team with appropriate training accomplish this task.

Please note that many studies approved at RUBIC have not been required to provide a read of potential incidental findings. However, discussions with the RU-New Brunswick IRB makes it unlikely that studies being performed at CAHBIR will be approved without a plan in place for handling incidental findings.

Template IRB protocol language regarding CABHIRS standard approach:

*“Incidental findings*: It is CAHBIR’s practice to show subjects a picture of their brain after the scan is completed. However, CAHBIR will avoid showing a participant a slice (2-D image) that reveals an incidental finding that could be reflective of a current or future neurological problem during that post-scan review. Any incidental finding that might reflect a current or future neurological problem will be read by a neuroradiologist (through a contract with University of Radiology). If the neuroradiologist determines that the participant should seek further evaluation or medical help, this information will be provided to the subject by the PI or a doctoral level team member who has been more closely working with the participant on the study. This communication will take place either by phone or preferably with a videocall that allows the PI to show the subject the incidental finding. (Note if PI is not an MD, the PI will make it clear that they are not a medical doctor or expert on the condition and therefore cannot give medical advice. After the call, the research team will email the patient the neuroradiologists report. In cases where a referral is needed by the subject, the PI will provide a recommendation to an appropriate doctor within the RWJ Health system and give the subject the ability to request the scans be provided to a doctor of their choosing (after completing a release of information form).

Only scans with the appearance of a potential incidental finding will be read by a neuroradiologist. CAHBIR adopted this approach after reviewing policies at peer institutions. Multiple institutions with existing imaging centers have grappled with the question of how to handle incidental findings appearing on research scans. The challenge is the balance between the duty to notify a participant if they have an abnormality that may require intervention and the excessive expense of having every scan read by a neuroradiologist. The problem with a requirement to have a radiologist read every scan is that the cost rapidly becomes excessive, especially when less than 2% of scans of non-neurological populations warrant review. Moreover, most of the incidental findings in this population require no action (benign cysts, as opposed to neoplastic tissues or lesions).

A survey of major MRI centers reveals great heterogeneity on how to balance the duty to warn the participant and the excessive costs of neuroradiological reads. Several of our peer institutions absolve themselves of responsibility to inform participants of any incidental findings. For instance, consent forms at Harvard explicitly state that the scan is being performed for research purposes only and that participants will not be informed of any abnormalities. Multiple of our peer institutions have no requirement of a radiologists read (e.g., Duke, NYU), and indeed RUBIC, which is the sole site in the Rutgers system that has routinely performed MRI on healthy individuals does not have a policy of radiologist reads, and says nothing about how incidental findings will be handled in their consent form or standard procedures documentation.

While we generally aim to limit inconsistencies across Rutgers’ sites and protocols, we are proposing a procedure that takes responsibility for a duty to inform participants, while limiting the prohibitive expense of having all scans read when the vast majority of participants have no incidental findings.

In designing the present approach, CAHBIR followed the influential guidance provided by Wolf et al. (2008). After providing a thorough review of research ethics on the handling of incidental findings, they articulate that protocols must have a plan for handling incidental findings, including consulting with a radiologist (or other relevant expert) when there is the appearance of an incidental finding. The radiologist is consulted to determine if the observed incidental finding is indeed of note, and if it is likely to have enough health impact to warrant disclosure to the participant.

CAHBIR’s approach is to maximize detection of incidental findings, while not making the cost of scanning so high that researchers actually scan fewer subjects or chose to scan at a different location within or outside of the Rutgers system where it is cheaper because there is no read of any scans at all regardless of the presence of a potential incidental finding. Such a situation actually results in fewer participants receiving warning about a potentially serious problems and fails to serve the participants best interest. Following the guidance of Wolf et al (2008), we believe that the duty to the participants arises *if* a potential incidental finding is seen. To maximize detection of such cases, we apply a two-tiered approach to screening and evaluation of incidental findings. First, a clinically trained brain MR-technician surveys the scan (typically while the participant is in the scanner). The MRI technologist will have received their certification in accordance with the American Registry of Radiologic Technologists, which includes requirements of training in neuroanatomy and a clinical internship to ensure that they have sufficient exposure to neuropathology. The technologist will receive a one-on-one review of cases with a neuroradiologist in the RWJMS to ensure that they understand precisely what the radiologist wants them to screen for. If the scan is run by anyone other than a certified brain MRI technologist, the scan will be screened by the certified MRI technologist, or a neuroradiologist within 10 days of scanning.

It is noted that the idea that a neuroradiologist should read every scan is predicated on a questionable assumption that a radiologist will be better at detecting a problem than a technician. While some scans in this protocol include T2-T2 Flair scans, which are highly useful at detecting pathology, most of the sequences that will be focused on here are not. The sequences used for functional MRI cannot be used to detect pathology. The T1-weighted scans that are collected with almost every study to define neuroanatomy are not useful for detecting most clinically relevant pathology other than large volume occupying masses, or hydrocephalus. These large-scale effects are easily identifiable by a technician (and by most investigators with substantial experience with brain MRI research). The radiologist is clearly needed to make diagnoses and recommendations in such cases, but their level of expertise is not necessary in order to be able to detect a gross abnormality on a T1 image. Smaller possible incidental findings on a T1 are of questionable significance and are generally not interpretable in the absence of a more thorough set of clinical scans. There is a substantial risk of costly false-positives in interpreting such findings, and there is a substantial cost to participants in terms of anxiety and medical costs for paying for those further clinical scans (see Royal and Peterson, 2015 for a discussion of the risks associated with “searching for pathology” on research scans). Thus, for most research studies in which the only clinically interpretable scan is a T1-wieghted image, there is unlikely to be a benefit to participants of having their scan read by a neuroradiologist. Moreover, informing participants that their scans will automatically be read by a neuroradiologist may give them a false impression that the assessment was equivalent to a clinical exam, and that they have been ruled free of some form of neuropathology that was not in fact assessed. Combined with the burdensome cost on the research enterprise that acts to lower the number of studies conducted, and as a consequence lower the number of true positives detected, we believe that cost-benefit analyses strongly argues for an approach in which the radiologist is consulted when there is the appearance of a possible incidental finding, rather than an approach in which radiologists view large numbers of scans on which there is neither an abnormality nor an ability to detect most forms of neuropathology.

It is unlikely, but possible that a participant would have an emergent situation in which an immediate neuroradiological read would prove useful. A medical emergency happening while the person is in the scanner or scanner suite would automatically lead us to call for an ambulance to take the person to a local hospital in New Brunswick. Nevertheless, it is feasible that we happened to collect a useful scan-type and the person by chance appears to have a cerebrovascular accident during or immediately following the scan session, we would provide images to the patient that can travel with the patient to the emergency room. Note, in such a case, the read of the images would be the responsibility of the hospital rather than the researcher because the subject would already be under the hospital’s care and there would be no need for a secondary evaluation by University Radiology. Note in such cases we would not ask the subject to complete a request for release of information since the images would be given directly to the patient if they are conscious, and the importance of providing the emergency room doctors the information would override privacy concerns if the person was incapable of signing a request for release of information.”

Template ICD language regarding incidental findings:

Incidental findings: The MRI exam could reveal an abnormality in your brain. This finding may be distressing to you. Scans at the Center for Advanced Human Brain Imaging Research (CAHBIR) are screened for abnormalities. If there is any sign of an abnormality, the scan data is reviewed by a certified neuroradiologist through a contract with University Radiology Group (URG). The neuroradiologist provides a brief written evaluation that includes their recommendation as to whether any potential abnormality is clinically significant, and if it is, provides a recommendation for referral or further evaluation. The study PI, Dr. Zald, is responsible for communicating this finding to you if it is deemed clinically significant.

**Transferring data from the scanner and Flywheel**

CAHBIR has contracted with Flywheel.io in order to provide a mechanism for transferring and archiving data in a secure manner that provides lab-specific restrictions to datasets. Data archiving is included in the cost of scanning at CAHBIR. Unless there is an explicit request to not utilize Flywheel, data from each study session will automatically be uploaded to Flywheel, and will become accessible to the investigator, a short time after the study session is completed.

Because our Flywheel implementation resides in Google Cloud Service, it is necessary to include in section 6.2 Data Security of your IRB protocol the following statement.

“With approval from the Rutgers IT Risk assessment team, CAHBIR has contracted with Flywheel.io and Google Cloud Services to allow data transfer from CAHBIR to the PI’s lab and basic image processing and archiving. The cloud-based service is both dbGAP and HIPPA compliant, with data access restricted to the PI’s study-specific research team using Rutgers SLA authentication of authorized users. Data submitted to Flywheel never include any names, social security numbers or medical record numbers”